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a single-blinded randomised controlled trial

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Home-based exergaming was safe and significantly improved 6-min walking distance in prostate cancer patients: a single-blinded randomized controlled trial

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Abstract

Objectives: To explore the effects of 12 weeks of unsupervised home-based exergaming (i.e. technology-driven exercise) compared to usual care on physical function, body composition, quality of life (QoL) and fatigue in prostate cancer patients (PCa) on androgen deprivation therapy (ADT).

Patients and methods: In an assessor-blinded randomized controlled trial, 46 PCa patients (+65 years of age) with locally advanced or advanced stage disease undergoing ADT were randomized to 12 weeks of unsupervised home-based exergaming, or usual care from two hospitals in Denmark. The primary outcome of the study was 6-minute walking test (6MWT). Secondary outcomes were leg extensor power (LEP), body composition (lean- and fat- mass), self-reported physical functioning and global health status (EORTC QLQ-C30), QoL (FACT-P) and fatigue (FACT-F).

Results: Significant improvement was seen in the exergaming group compared to the usual care group in the primary outcome 6MWT (mean difference: 21.5 meters; 95% confidence interval (CI) 3.2 – 39.9; p=0.023). No between group differences were seen for LEP (p= 0.227), lean body mass (p=0.100), fat body mass (p=0.092), self-reported physical functioning (p=0.084) and global health status (p=0.113), QoL (p=0.614) and fatigue (p=0.147).

Conclusion: 12 weeks of unsupervised home-based exergaming had an effect on the primary outcome 6MWT in PCa patients receiving ADT. However, no significant effects were found in secondary outcomes. The exergaming intervention appeared safe and could be an alternative to traditional aerobic and resistance training in this patient group.

Key words: Prostate cancer, Androgen deprivation therapy; Home-based exercise; Exergaming; Fatigue; Quality of life.

Introduction

Androgen deprivation therapy (ADT) constitutes a central component in the treatment of metastatic prostate cancer (mPCa) and as adjuvant therapy to radiation in patients with intermediate or high-risk localized disease. Unfortunately, ADT has several adverse effects: reduced physical function shown by reduced grip strength, and decreased score on the Timed Up and Go test [1], Loss of muscle and bone mass [2], decreased (QoL) [3], and increased fatigue [4] are frequently observed. Fortunately many of these ADT related complaints appear to be counteracted by exercise interventions. Systematic reviews have documented beneficial effects of combined aerobic and resistance exercise interventions on ADT-related adverse effects in PCa patients [5–9]. However, the majority of exercise studies have been conducted in supervised facilities (i.e. a hospital clinic or a fitness centers), making the interventions inconvenient to patients due to travel distance and fairly costly due to the involved health professionals. Therefore, as an alternative, a few studies have explored home-based unsupervised walking interventions on PCa patients receiving ADT and have found positive results on vitality and body composition [10–12].

Marked advances in gaming technology, e.g. the introduction of the Nintendo Wii balance board in 2008 and the Microsoft Kinect Camera in 2010, has led to a new way of controlling and playing games. This new way is by standing up and moving the body in order to control an avatar displayed on a television screen and has been labeled “exergaming”. Through history computer games have been controlled while sitting down using a handheld controller or a keyboard. This new way of exercising called exergaming has already been studied in other cancer patients than PCa patients and have shown alleviating fatigue, improving

functional performance [13], maintaining physical performance during chemotherapy [14] and increasing physical activity during hospitalization [15]. One home-based exergaming study in post-surgical lung cancer patients showed reduced fatigue, improved functional status and QoL [16]. Thus, in the present study we aimed to explore the effects of 12 weeks of unsupervised home-based exergaming in PCa patients receiving ADT compared to usual care. The effects were evaluated between the groups primarily through the 6MWT and secondary through leg extensor power (LEP), body composition (lean- and fat- mass), physical functioning and global health status (EORTC QLQ-C30), and QoL (FACT-P), and fatigue (FACT-F).

Material and Methods

Study Design and Recruitment

In an assessor-blinded randomized controlled trial 23 patients were assigned to the intervention group (Exergaming) and 23 patients to a usual care group. Eligible patients were Danish speaking PCa patients receiving continuous ADT for at least three months prior to inclusion, cognitively well-functioning and able to answer questionnaires and comply with the exercise program according to instruction, and performance status 0-1. For safety reasons, progression of PCa disease or development or progression of bone pain due to bone metastases during the intervention period would discontinue patients. Between February 2015 and January 2017 we included 46 patients from the urological outpatient clinics at Regional Hospital Holstebro, (*n*=32) and Regional Hospital Viborg (*n*=14), Denmark. All study procedures were conducted at Regional Hospital Holstebro. The study was registered at Clinical trial.gov, ID: NCT01762241 and approved by the Regional ethical committee Central Denmark Region, protocol no. 1-10-72-195-14 as well as by the Danish Data Protection Agency protocol no. 1-16-02-536-14.

Written informed consent was obtained from all patients prior to inclusion in the study. The study protocol has previously been published [17]. Remaining outcomes stated in the protocol paper will be published elsewhere.

Sample size calculation

Based on pilot testing our sample size calculation assumed that the exergaming intervention would lead to a between group difference of 100 meter with a standard deviation of 84.5 in the 6MWT at 12 weeks follow-up favoring the exergaming group (one-way). Further, we based our sample size calculation on an alfa level of 5 % and a beta level of 90 % and a dropout rate of 30%. With these assumptions 48 patients needed to be enrolled to attain 34 completed patients.

Randomization and blinding

The principal investigator enrolled each subject. Randomization in blocks of 8-10 patients was used to secure a balanced allocation of patients (1:1) to either intervention or usual care. For randomization purposes, sealed, opaque envelopes with equal allocation to each group were used in an amount consistent to the number of subjects randomized in each block. The research assistant supervised each subject picking an envelope. All physical and functional outcomes were assessed by an experienced physiotherapists blinded to the group allocation.

Intervention

The intervention group received 90 minutes individual instruction by a physiotherapist prior to the homebased exergaming with the Xbox 360 Kinect system (Microsoft, Redmond, WA, USA). Patients were instructed to do aerobic and strength exercise for one hour, including a warm up and cool down period, three times a week for 12 weeks using the Your Shape

Fitness Evolved 2012, Sport and Adventure games at their own convenience. Free weights of 0.5, 1.0 and 2.0 kg were used to support the gradually increasing exercise intensity of the Fitness Evolved 2012 game. Throughout the study, i.e. from baseline to week24 (w24), each patient kept a diary of his self-reported exercise. No other study procedures were scheduled between w12 and w24.

Until the post-intervention assessments at w12 the research assistant contacted the intervention group by telephone every second week to ensure compliance, registration of adverse events, and changes in medication. Between w12 and w24 the patients were not contacted by the research assistant.

Usual care

Usual care group patients were instructed to continue their normal daily activities throughout the study and each patient kept a diary of his self-reported exercise. As the usual care group was not expected to increase activity level until the post-intervention assessments at w12, the research assistant contacted this group by telephone every fourth week to ensure compliance, registration of adverse events, and changes in medication. Between w12 and w24 the patients were not contacted by the research assistant.

At w24 patients in the usual care group were given advice on exercise according to existing guidelines, recommending 150 minutes of aerobic exercise of moderate intensity or 75 minutes of vigorous intensity every week, combined with two sessions of resistance exercise and stretching[18].

Primary and secondary Outcomes

Primary and secondary outcomes were measured at baseline and at w12 (Table 1).

The validated 6MWT was used to assess physical function, which was the primary outcome.

A power rig (University of Nottingham Medical School, Nottingham, UK) was used to assess leg extensor power (LEP). Body composition was assessed using the Bodystat® Quadscan 4000 bioelectrical impedance analyzer. The physical functioning and global health status subscales of the quality of life questionnaire EORTC QLQ-C30 and Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaires were used to assess self-reported QoL. The fatigue subscale of the Functional Assessment of Cancer Therapy - Fatigue (FACT-F) questionnaire was used to assess fatigue using a fatigue-defining cut-off score of < 34[19]. Godin Leisure-Time Exercise Questionnaire score was used at baseline, w12 and follow-up at w24 (intervention group only) to track changes in physical activity level. High score is correlated with physical activity and low score reflects physical inactivity.

Exercise intensity during exergaming as well as physical activity (i.e. accelerometry) was not measured.

Statistical analysis

Data were analyzed using Stata version 13. The primary analysis was a modified intention-to-treat (mITT) population consisting of individuals with both baseline and w12 measurements. We performed a complete case analysis comparing groups according to the original random allocation.

For all outcome measures a linear regression analysis was conducted to evaluate differences in effects between groups adjusting for the baseline values as well as treatment duration below or above 365 days (ADT), BMI, and activity level based on the Godin Leisure-Time Exercise Questionnaire score. All values are shown as the mean and 95 % confidence interval (CI). A *P* value of less than 0.05 was considered to be statistically significant.

Results

As shown in the CONSORT diagram (Figure 1), two patients in the intervention group and three patients in the usual care group did not complete the study, resulting in 91% completing patients in the intervention group and 87 % in the usual care group. One of the remaining 20 patients in the usual care group sustained a muscle strain during the physical tests at baseline and refused to repeat these tests at post-intervention.

There were no significant between-group differences at baseline (Table 2). A panel of biochemical routine measurements, including plasma potassium, sodium, calcium, albumin-adjusted calcium, albumin, creatinine, glomerular filtration rate, CO_2 and hemoglobin, were analyzed and remained stable during the study (data not shown).

Neither cardiovascular nor skeletal related events (i.e. pathologic fracture, spinal cord compression, necessity for radiation to bone (due to pain or impending fracture) or surgery to bone) were observed during the study.

Primary outcome

At w12, the adjusted analysis for the 6MWT showed a statistically significant difference favoring the intervention group, with an estimated 4.2 % improvement of 21.5 meters (95 % CI 3.2 to 39.9, p=0.023) compared to the usual care group (Table 3).

Secondary outcomes

LEP

The LEP test showed no statistical significant improvement in the intervention group compared to the usual care group in the adjusted analysis (mean difference 20.3 w; 95 % CI -13.2 to 53.8 p= 0.227) (Table 3).

Body composition

At w12 lean mass increased numerically (mean difference 0.91 %; 95 % CI -0.2 to 2.0; p=0.100) and fat mass decreased numerically (mean difference -0.9 %; 95 % CI -2.0 to 0.2; p=0.092) when comparing the groups (Table 3). However, neither difference reached the level of statistical significance.

Quality of life and Fatigue

After 12 weeks the intervention group had the same QoL (FACT-P) as the usual care group (mean difference 2.1 points; 95 % CI -6.3 to 10.6 p=0.614). Numerical, but insignificant increases were observed in physical functioning (+7.7 %; mean difference 6.2 points; 95 % CI -0.9 to 13.3; p=0.084) and global health status compared to the usual care group (mean difference +8.8 points; 95 % -2.2 to 19.7 p=0.113) (Table 3).

Fatigue did not improve in the intervention group compared to the usual care group at w12 (mean difference 2.4 points; 95 % CI -0.9 to 5.7 p=0.155) (Table 3).

The intervention was well-tolerated by all patients. However, when exercising one patient in the intervention group experienced severe non-heart-related chest pain due to surgical clips in thorax leading to discontinuation from the trial. No other adverse events from the intervention led to withdrawal or discontinuation of patients from the study.

Physical activity level

The Xbox Kinect, games and dumbbells were given to the intervention group to keep, and thus we investigated any change in physical activity level in this group after the w12 assessments. Figure 2 shows that the intervention group voluntarily continued to increase physical activity level throughout the study displayed by an increase of 8.5 points on the

Godin Leisure-Time Exercise score at w12 and an increase of 15.2 points at w24 compared to baseline. However, the increase was not statistically significant.

Compliance to the intervention is shown in Figure 3. Each patient reported exergaming on average 153.5 minutes per week between baseline and w12; however, the protocolled exercise duration was 180 minutes per week.

Discussion

This is the first study to examine the effects of 12 weeks of unsupervised home-based exergaming using a Microsoft Xbox 360 Kinect system in PCa patients receiving ADT compared to usual care. Our main finding was that the exergaming intervention significantly improved the six minutes walking ability compared to the usual care group. Surprisingly, in all of our secondary outcomes, we found no significant change between groups. However, we did see trends favoring the exergaming group as LEP increased by 7.6 % and fat mass decreased by 3.0 % compared to the usual care group. In addition, during the post-intervention period (from week 12 to 24) we did not expect the exergaming group to continue to be physically active, however the Godin score proved otherwise and peaked at week 24. Finally, the current exergaming intervention appeared safe in PCa patients on ADT, as no incidents of cardiovascular or skeletal related events were reported.

Walking speed has a potential to predict future health status, functional decline, and mortality[20], and as PCa patients can live for decades due to new therapies, the 6MWT could be used as a reliable measure in the clinical setting as well as in clinical research when health promoting interventions are evaluated. We found a significant difference of 21.5 meters (p=0.023) between groups favoring the exergaming group in the 6MWT, but a *post hoc* effect size calculation (cohen's d) showed a small to medium effect. Unfortunately, no studies on minimal clinically important difference (MCID) have been performed on PCa

patients to place our results in context. However, a recent systematic review by Bohannon *et al* explored MCID in adults with different pathology and found the MCID distance on the 6MWT to be somewhere between 14.0 to 30.5 meters [21]. With this in mind our 21.5 meters might have had a clinical impact on our patients. On the other hand, when comparing our results to other studies which have looked at supervised and unsupervised aerobic and/or resistance exercise [7,11,22–26] our results appear fairly modest. In example, Gaskin *et al* found a significant increase of 49.98 meters in the intervention group compared to the control group [25], and in the study by Hojan *et al* [23] the intervention group increased walking distance while the control group gradually decreased walking distance leading to an improvement of 27.39 meters favoring the intervention group. Thus, the exergaming intervention did not reach the same effect on walking distance as supervised aerobic and resistance. This might be explained by the design of the study, as there was no supervision after the instructions at baseline, and thus the patients did not get any feed-back on their exercise level and performance other than what the technology provided. Exergaming technology offers some sort of feed-back, reward system and goal-setting and thus motivates PCa patients to exercise, which is considered important in cancer rehabilitation [27]. However, exertion is a self-perceived phenomenon, and it is unclear whether patients performed at their maximum during exergaming without supervision. Nevertheless, patients were in contact with a research assistant on regularly basis, and thus the effort put in to exergaming could have been influenced positively.

The lack of ability to show any significant improvement in self-reported physical functioning, general health status and FACT-P was supported by findings in previous studies, where supervised exercise was demonstrated to be more efficient than home-based exercise [23,28]. However, previous conflicting results have been reported with regards to this outcome measure [29]. The exergaming intervention showed an improvement of 1.74 % on the FACT-

P total score, which is less than previous shown 3-10 % improvements in adjusted between group differences in aerobic and resistance exercise interventions [28]. As the most beneficial exercise intervention to improve the FACT-P score has yet to be clarified, exergaming needs further investigations as the technology offers both single-player and multiplayer games, where patients can have fun while exergaming together. Thus, it can be investigated whether increase in QoL is dependent on, whether patients do exergaming together or alone as football due to its group-based nature has shown positive results on mental and social well-being [30].

The fatigue score was generally high in our patients, implying the absence of fatigue at baseline and this may explain that exercise was unable to improve it any further. Most likely, the high baseline fatigue score is explained by a selection bias when recruiting study participants. We believe the physically demanding intervention attracted primarily physically fit patients, as 78 eligible patients refused to participate.

Contrary to previous findings [31,32] the effect on body composition was negligible. We believe this reflects an insufficient intervention with regard to resistance exercise as well as the lack of continually reminding the patients about the progressive demand to perform moderate to high intensity exercise. In addition, exercise intensity is a subjective experience and some patients might not have challenged themselves as much as an exercise physiologist or physiotherapist would have done in a supervised setting. Especially the patients with bone metastases might have exercised more careful in respect of sustaining a fracture or injury when left on their own.

The observed numerically increase in leg muscle power in the intervention group was less than reported in supervised exercise studies [28], presumably due to factors as described above.

The documented average minutes spent exergaming per week did not comply with the protocolled 180 minutes. Thus it is unknown whether the reporting was unreliable or a true inadequate compliance explained by lack of interest, priority or a too demanding intervention. As previously published [33] and recommended by Kahan *et al* [34], our analysis were adjusted to minimize any confounding impact on the outcomes, since randomization does not guarantee balance in important baseline covariates. In particular, we had expected physical activity to be a pronounced prognostic factor, however, this covariate turned out to be balanced at baseline (Table 2).

The very low attrition rate, with 91% completing patients in the intervention group and 87% in the usual care group, implies an applicable study design for use in future studies. Nevertheless, a few limitations need to be taken into account in this study. The true effect of 21.5 meters was less pronounced than the estimated 100 meters increase in the intervention group compared to the usual care group. However, this estimate was unrealistic to reach as it presumably would have demanded changes in walking technique (i.e. posture, stride and arm motion) in addition to exergaming. Though, the statistical significant result of the 6MWT needs to be confirmed in larger multicenter studies, as the risk of type II error increased in this study. The sample size of 46 patients was based on the expectation that it would be unrealistic to recruit a significantly large study population within the actual time frame. Another limitation, well-known in exercise trials, is that the current study was unavoidably affected by a selection bias. Firstly, the consent to participate required a surplus of mental and physical energy. This notion was supported by the high baseline score on the fatigue subscale and accordingly, our data cannot be extrapolated to more severely affected PCa patients. Secondly, all patients were from rural and urban areas, most of them married and holding a bachelor degree, making the study population quite homogenous but concurrently less representative for the entire background population of PCa patients.

Conclusions

To the best of our knowledge, this is the first randomized study to investigate the effects of unsupervised home-based exergaming in PCa patients undergoing ADT. The study showed a significant but modest improvement in 6MWT favoring the exergaming group. In addition, results showed that the intervention group kept being physically active during the post-intervention period, where no influence from health care professionals was present. In addition, no significant effects in any of the secondary outcomes were found. The exergaming intervention appeared safe and could be an alternative to traditional aerobic and resistance training in this patient group.

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Conflict of interest

No potential conflict of interest was reported by the authors.

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Legends to figures and tables:

Figure 1 - CONSORT diagram of recruitment and loss to follow-up through the trial

One patient in the intervention group developed non-cardiac related chest pain during exercise and one withdrew consent. In the control group one patient violated the allocated intervention, one suffered a severe traffic accident, and another did not accept the allocated intervention.

Figure 2 – Mean score on the Godin Leisure-Time Exercise Questionnaire

Mean score on the Godin Leisure-Time Exercise questionnaire reflecting physical activity level throughout the study. Only data on the exergaming group at 24 weeks follow-up.

Figure 3 – Average minutes spent exercising per week for all patients in the exergaming group.

Table 1 – Assessment schedule

All assessments were conducted at three time points over the course of six months.

At baseline patients allocated to the intervention group attended the clinic an additional two times for instructions regarding the home-based exercise program.

Table 2 – Baseline characteristics of study participants

ADT=Androgen Deprivation Therapy.

Data for continuous variables were assessed as Mean (SD) using independent sample t-test.

Non-normal distributed continuous data were assessed as median (IQR) using Mann-Whitney test.

Data for categorical variables are presented as frequency (%) using Fisher's exact test.

There were no statistical significant differences between groups at baseline ($p > 0.05$ for all variables).

T stage was determined at time of PCa diagnosis. The presence of metastases was determined when ADT was initiated.

Table 3 – Between group changes adjusted for baseline score on the Godin Leisure-Time Exercise Questionnaire, ADT treatment duration </> 365 days and BMI

*Baseline data was not available from one withdrawn patient in the usual care group.

Table 1 – Assessment schedule

All assessments were conducted at three time points over the course of six months.

At baseline patients allocated to the intervention group attended the clinic an additional two times for instructions regarding the home-based exercise program.

	Week -2/baseline	Week 0-12	Week 12	Week 24
Inklusion and randomization	x			
Assessments: 6MWT LEP Body composition	 x x x		 x x x	
Questionnaires: EORTC QLQ C-30 scales: Physical functioning and General Health status. FACT-P FACT-F	 x x x x		 x x x x	
Godin Leisure-Time exercise questionnaire*	x		x	x
Exergaming three times per week/180 min. (intervention group) Usual activity level (usual care group)		x x		

*At week 24 the Godin Leisure-Time exercise questionnaire was handed out to the intervention group only.

Table 2 – Baseline characteristics of study participants

	Intervention group	Usual care group
	(n=23)	(n=23)
	mean ± (sd) n (%) median (IQR)	mean ± (sd) n (%) median (IQR)
Age	67.6 (4.6)	69.8 (4.4)
Marital status:		
Single	4 (17 %)	3 (13 %)
In relationship, not married	0 (0 %)	2 (9 %)
Married	18 (78 %)	18 (78 %)
Divorced	0 (0 %)	1 (4 %)
Educational level:		
Primary school	1 (4 %)	0 (0 %)
High school	1 (4 %)	2 (9 %)
Short-length higher education	5 (22 %)	6 (26 %)
Medium-length higher education	14 (61 %)	14 (61 %)
University degree	2 (9 %)	1 (4 %)
Weight (kg)	93.2 (11.4)	88.3 (12.1)
BMI	29.8 (0.6)	29.1 (0.7)
Waist circumference (cm)	110.1 (8.4)	109.6 (9.6)
Gleason score:		
Gleason 6	1 (4 %)	3 (13 %)
Gleason 7	11 (48 %)	5 (22 %)
Gleason 8-10	11 (48 %)	14 (61 %)

Not available	0 (0 %)	1 (4%)
T-Stage:		
T1c-T2a	6 (26 %)	1 (4 %)
T2b	5 (22 %)	2 (9 %)
T2c-T3c	12 (52 %)	19 (83 %)
Tx	0 (0 %)	1 (4 %)
Metastases		
Bone metastases	10 (43 %)	6 (26 %)
Lymph node metastases	2 (9 %)	1 (4 %)
M0, prior radiation therapy + ADT	11 (48 %)	16 (70 %)
ADT < 365 days	7 (30 %)	8 (35 %)
ADT > 365 days	16 (70 %)	15 (65 %)
Cardiovascular disease	16 (70 %)	17 (74 %)
PSA (µg/L)	0,1 (0.1-0.3)	0.1 (0.1-0.2)
Godin score	29.3 (29.2)	27.3 (21.8)

ADT=Androgen Deprivation Therapy.

Data for continuous variables were assessed as Mean (SD) using independent sample t-test.

Non-normal distributed continuous data were assessed as median (IQR) using Mann-Whitney test.

Data for categorical variables are presented as frequency (%) using Fisher's exact test.

There were no statistical significant differences between groups at baseline ($p > 0.05$ for all variables).

T stage was determined at time of PCa diagnosis. The presence of metastases was determined when ADT was initiated.

Table 3 – Between group changes adjusted for baseline score on the Godin Leisure-Time Questionnaire, ADT treatment duration </> 365 days and BMI

	Baseline		Week 12		Adjusted group differences in mean change over 12 weeks		
	Intervention group (*n*=23)	**Usual care group (*n*=23)**	**Intervention group (*n*=21)**	**Usual care group (*n*=20)**			
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean**	**95%CI**	***p*-value**
6-min walk test (m)	526.8 (65.6)	497.3 (79.8)	556.1 (59.0)	500.8 (80.6)	21.5	3.2 – 39.9	0.023
Leg extensor power (w)	319.3 (102.4)	267.3 (108.2)	349.2 (93.0)	272.3 (95.8)	20.3	-13.2 – 53.8	0.227
Lean mass (%)	71.1 (3.6)	70.6 (3.7)	71.2 (3.9)	70.0 (4.3)	0.91	-0.2 – 2.0	0.100
Fat mass (%)	28.9 (3.6)	29.4 (3.7)	28.8 (3.9)	30.0 (4.3)	-0.9	-2.0-0.2	0.092
Physical functioning (points)	89.3 (9.8)	86.4 (12.0)	93.7 (9.8)	83.3 (18.8)	6.2	-0.9 – 13.3	0.084
Global health status (points)	67.0 (20.2)	67.4 (23.4)	81.4 (16.9)	72.5 (20.4)	8.8	-2.2 – 19.7	0.113

*FACT-P questionnaire (points)	118.7 (14.2)	119.4 (17.4)	123.1 (13.9)	120.7 (18.0)	2.1	-6.3 – 10.6	0.614
FACT-F subscale (points)	43.8 (5.4)	41.1 (8.6)	45.9 (6.7)	40.0 (10.3)	2.4	-0.9 - 5.7	0.155

* Baseline data was not available from one withdrawn participant in the usual care group

Figure 1 - CONSORT diagram of recruitment and loss to follow-up through the trial

One patient in the intervention group developed non-cardiac related chest pain during exercise and one withdrew consent. In the control group one patient violated the allocated intervention, one suffered a severe traffic accident, and another did not accept the allocated intervention.